Please add new claim 40 as follows:

B7 cont

- - 40. (new) The method of claim 38 wherein the diagnostically effective compound is an iodinated contrast agent, MR active agent, or ultrasound contrast agent imageable marker. - -

Remarks

Claims 1-37 are pending in the captioned application. Claims 8-37 have been withdrawn from consideration. Applicants have cancelled claims 1 and 7, without prejudice, amended claims 2-6, and have added new claims 38-40. Applicants respectfully submit that claims 38-40 are based on cancelled claim 1, and that, support is presented in the specification for the claims. Applicants respectfully request entry of the amendments.

The Examiner has rejected claims 1-7 under 35 U.S.C. 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention", objecting to the use of certain terminology in the claims.

In response, Applicants have cancelled claim 1, without prejudice, and have substituted claims 38-40 therefore. Applicants believe that these claims are clear and unambiguous. Applicants have also amended claims 2-6 to recite dependency on claim

38, amended claim 4 to remove the term "vascular bed" and have cancelled claim 7, without prejudice.

In view of the foregoing, Applicants respectfully assert the Examiner's rejection cannot be sustained and should be withdrawn.

The Examiner has rejected claims 1-7 under 35 U.S.C. § 102(b), as being anticipated by Sumiaki (Japanese Patent 63255231). Specifically, the Examiner states, "Sumiaki discloses a method of embolus therapy comprising administering a composition comprising particles of hydroxyapatite having a size of 10 to 1000 um, see pages 3-4. The method further includes diagnostic imaging to detect the location of the embolus, wherein the particles have contrast media function ... ."

In response, Applicants respectfully assert that the Examiner has not appreciated the differences between the Sumiaki reference and the instant invention. More specifically, as disclosed in the Sumiaki Japanese patent application, the embolus agents disclosed in the reference are intended to be **therapeutic** agents which **include a therapeutic antineoplastic agent** (see e.g. page 5). Such is not the nature of the instant invention, which is a method for introducing contrast agents to a particular site of interest using embolus generating agents. While Applicants concede that the Sumiaki reference does disclose the use of diagnostic imaging to detect the location of the embolus, there is no disclosure, nor even any suggestion, that the embolytic particles should contain a diagnostically effective compound for use in the inaging procedure. Indeed, no such agent is included as the Sumiaki reference discloses that the embolytic particles are to include the therapeutic (antineoplatic) composition to be delivered at the desired site.

In view of the foregoing, Applicants respectfully assert the Examiner's rejection cannot be sustained and should be withdrawn.

The Examiner has rejected claims 1-7 under 35 U.S.C. § 102 (b) as being anticipated by Tsuru (U.S. Patent 5,055,307). Specifically, the Examiner states, "Tsuru discloses a method of embolus therapy comprising administering a composition comprising particles of hydroxyapatite having the size of 5 to 1000 um, and performing diagnostic imaging to detect the location of the embolus … ."

In response, Applicants respectfully submit that, like the Sumiaki reference, the disclosure of the Tsuru reference is also directed to drug delivery at the site of the embolus, and **not the use of the embolytic particles containing a contrast agent for imaging purposes**. While Applicants concede that the reference suggests that the particles may be useful for imaging purposes, the reference neither discloses nor even suggests that the particles should be utilized to contain an imaging agent as in the instant invention. Indeed, at the sited portion of column 5, the patent specifically states "the drug delivery granules have no toxicity to a human body having excellent imaging property to an x-rays or ultrasonic waves, and can easily be traced after the application thereof (column 5, lines 30-35)", indicating that the particles themselves, and not a contained imaging agent, contribute to the imaging technique. Further, as in Sumiaki, it is disclosed that the granules may contain a drug component which is to be released at the site of the embolus (column 3, lines 54-70), indicating that there is no contrast agent to be contained, and that the particles themselves **may be administered in suspension with an iodine type contrast agent** (see e.g. example 1), which is further indication that the reference does not contemplate the inclusion of a contrast agent in the particles. Indeed.

Applicants respectfully assert there is no disclosure, nor even any suggestion, of the instant invention wherein the particles are used to contain the contrast agent.

In view of the foregoing, Applicants respectfully assert the Examiner's rejection cannot be sustained and should be withdrawn.

The Examiner has rejected claims 1-7 under 35 U.S.C. § 102 (b) as being anticipated by Okada (EP 470569). Specifically, the Examiner states, "Okada discloses a method of embolus therapy comprising administering a composition comprising particles having a size of 5 to 1000 um ... The particles comprise hydroxyapatite ... The particles may further comprise a contrast agent for imaging techniques ... ."

In response, Applicants respectfully assert that the Examiner has mischaracterized the disclosure of this reference. Specifically, at page 8, lines 34 et seq. The disclosure specifically states, "the intravascular embolizing agent of the present invention is used as it is, or by **dispersing, before or at the time of use in a** proper pharmaceutically acceptable character, for example, dispersing vehicle or **a contrast medium such as lipodol" (emphasis added).** Thus, it can be seen that the cited reference does not disclose the particles contain contrast agent, but rather (as was the case with the Tsuru reference, that the particles should be dispersed in a contrast agent, if desired for contrast purposes. Applicants respectfully assert that the instant invention is neither disclosed nor even suggested.

In view of the foregoing, Applicants respectfully submit the Examiner's rejections cannot be sustained and should be withdrawn.

The Examiner has rejected claims 1-7 as being unpatentable under 35 U.S.C. § 103, over any one of Sumiaki, Tsuru or Okada, in view of Meeh (WO 95/27437).

Specifically, the Examiner states, "Sumiaki, Tsuru and Okada disclose a method of embolus therapy comprising administering composition comprising particles by hydroxyapatite having a size of 5 to 1000 um, and performing diagnostic imaging to detect the location of the embolus, as discussed above." The Examiner concedes, "Sumiaki, Tsuru and Okada fail to specifically disclose that the hydroxyapatite has the specific formula as instantly claimed." The Examiner continues, "Meeh discloses that hydroxyapatite compositions, having the formula shown on pages 4-5, are especially useful for various methods of imaging ... ." The Examiner concludes, "It would have been obvious to one of ordinary skill in the art to use the hydroxyapatite compositions disclosed by Meeh as the hydroxyapatite compositions used in the methods disclosed by Sumiaki, Tsuru and Okada because Meeh teaches that such hydroxyapatite compositions ... are especially useful for various methods of imaging ... ."

In response, Applications reiterate the distinctions and remarks made with respect to the Sumiaki, Tsuru, and Okada references made supra. and respectfully submit that the citation of the Meeh et al. reference does nothing to remedy the deficiencies of the other references discussed above. Specifically, none of these references, alone or in combination with one another, disclose, nor even suggest, the method of the instant invention, which includes utilization of embolytic particles containing a contrast agent. The addition of the Meeh reference does nothing to remedy this.

In view of the foregoing, Applicants respectfully submit the Examiner's rejection cannot be sustained and should be withdrawn. Applicants believe that claims 2-6 and 38-40, as amended, are in allowable form and earnestly solicit their allowance.

Respectfully submitted,

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Claims (marked-up version showing amendment(s))

2. (once amended) A method as claimed in claim [1]38, wherein said particles are 5-25 micrometers in size.

3. (once amended) A method as claimed in claim [1]38, wherein said particles are 10-20 micrometers in size.

4. (once amended) A method as claimed in claim [1]38, wherein vascular collateralization of the embolized [vascular bed]vasculature is absent or sufficiently delayed such that said reduced perfusion is therapeutically effective.

5. (twice amended) A method as claimed in claim [1]38, wherein said water-insoluble particles comprise an insoluble phosphate salt of the formula

$$M_{10}(PO_4)_6A_z$$

wherein

M = Ba, Ca, Cd, Mg, Pb or Sr

A = OH^-, Cl^-, F^- or CO_2^{-2}

Z = 2 if A is univalent, 1 if A is divalent.

6. (twice amended) A method as claimed in claim [1]38, wherein said said insoluble phosphate salt is hyroxyapatite, $Ca_{10}(PO_1)_6OH_2$.

38. (new) A method of embolus therapy comprising a composition into the vasculature of a human or non-human animal subject, wherein said composition includes water insoluble particles 1-50 micrometers in size consisting essentially of a non-radioactive diagnostically effective compound or solution thereof encapsulated in a non-polymeric particulate matrix.

39. (new) A method of claim 38 wherein the non-polymeric particulate matrix is selected from the group consisting of insoluble metal oxides, insoluble metal salts, inert metals, glass, and ceramic particles.

40. (new) The method of claim 38 wherein the diagnostically effective compound is an iodinated contrast agent, MR active agent, or ultrasound contrast agent imageable marker.